

REMARKS

For convenience, in the present response, Applicants will refer the Examiner to disclosure in the specification by referencing the appropriate paragraph numbers of the Substitute Specification that was submitted on May 3, 2002.

Status of the claims

Upon entry of these remarks, claims 85-91, 118-124 and 148-182 will be pending in this application.

Applicants note that in the Clean Version of the Entire Set of Pending Claims provided with Applicants' Response and Amendment of May 3, 2002, Claim 124 was unintentionally labeled claim 125. Applicants have herein amended said claim to correct the erroneous numbering.

Claims 148 and 158 have been amended to recite "lymphocyte" in place of the word leukocyte. Support for these amendments may be found, for example, in the specification in paragraphs [0040], [0153], [0156], [0620] and Examples 6 and 7.

No new matter has been added by way of amendment, and Applicants respectfully request entry of these amendments

Request to Withdraw the "Finality" of the Office Action

The Office Action indicates that it is a "final" rejection of the pending claims. Attorneys for Applicant respectfully submit that finality is premature at this time. The Examiner's rejection under 35 U.S.C. § 112, first paragraph of claims 148-164, 181 and 182 regarding the term "leukocyte" was not previously presented in the prosecution of the present application. This rejection was neither necessitated by Applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR § 1.97(c) with the fee set forth in 37 CFR § 1.17(p) (See. M.P.E.P. § 706.07(a)). Applicants assert that a holding of "final" rejection at this time is premature since Applicants have not yet been able to address the new ground for rejection raised by the Examiner and because a clear issue regarding this ground for rejection has not been developed between the Examiner and Applicants prior to this action (see MPEP § 706.07). Accordingly, the finality of the outstanding Office Action is

improper. Applicants respectfully request that the finality of the Office Action mailed August 13, 2002, be reconsidered and withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

Claims 85-91, 118-124 and 148-182 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. More particularly, the Examiner alleges:

while being enabling for a method of inhibiting B-lymphocyte proliferation comprising administering to an individual, a therapeutically effective amount of an antagonistic antibody or a portion thereof that specifically binds a protein consisting of an amino acid sequence of amino acids residues 134-285 of SEQ ID No. 2, does not reasonably provide enablement for a method of inhibiting differentiation, and survival of B lymphocytes or proliferation, differentiation, and survival of 'all other' leukocytes, or treatment of 'any autoimmune diseases' (Paper No. 13, paragraph spanning pages 2-3).

This rejection can be separated into two distinct issues:

- A) Enablement of methods of inhibiting differentiation and survival of B lymphocytes or methods of inhibiting differentiation proliferation or survival of leukocytes other than B lymphocytes; and
- B) Enablement of claims directed to treating autoimmune diseases with antagonistic anti-Neutrokin- α antibodies.

Applicants will respond to each in turn.

A. The Examiner has newly rejected claims 148-164 and 181-182 under 35 U.S.C. § 112, first paragraph for lack of enablement, alleging that:

[t]he specification is not enabling for the practice of these claims because it is only the B lymphocyte proliferation that the instant Neutrokin- α predictably stimulates and not proliferation of all leukocytes. (Paper No. 13, page 5, lines 19-22).

Preliminarily, Applicants point out that the claims have been amended so as to replace the term "leukocyte" with the term "lymphocyte." The Examiner has acknowledged that the specification is enabling for the inhibition of B lymphocyte proliferation by antagonistic Neutrokin- α antibodies. Thus, Applicant will address this rejection only insofar as

necessary to show that the full scope of inhibition of lymphocyte proliferation, differentiation or survival is enabled.

Applicants respectfully disagree with the Examiner's assertion that methods of inhibiting lymphocyte proliferation, differentiation or survival are not enabled because "it is only the B lymphocyte proliferation that the instant Neutrokin- α predictably stimulates and not proliferation of all leukocytes."

The Examiner appears only to accept the enablement of claims directed to the inhibition of B cell proliferation by antagonistic antibodies of the invention due to the presence of a working example, Example 7, showing that Neutrokin- α protein stimulates B cell proliferation (see, Paper No. 13, page 4, line 12). As an aside, Applicants note that Example 7 also provides a working example for stimulation of B cell differentiation because administration of Neutrokin- α to mice results in an increase in the population of terminally differentiated plasma cells (CD45R(B220)^{dull}, ThB^{bright} cells) accompanied by an increase in serum immunoglobulin. Regardless, Applicants remind the Examiner that working examples are not required to satisfy the enablement criteria of 35 U.S.C. § 112, first paragraph. (See, M.P.E.P. 2164.02, "Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an Example is disclosed....because only an enabling disclosure is required, applicant need not describe all actual embodiments."). Applicants submit that the specification is enabling even in the absence of Example 7.

Applicants respectfully remind the Examiner that the test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988). The enablement requirement of the first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. How such teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective truth or accuracy of the statements relied upon therein for enabling support and it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement of the

presumptively accurate disclosure. *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992); *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971); *In re Brana*, 51 F.3d 1560 at 1566 (Fed. Cir. 1995).

Applicants point out that the specification discloses that Neutrokin- α promotes lymphocyte proliferation, differentiation, and survival (see e.g., paragraphs [0153], [0154] and [0156] and Examples 6 and 7, particularly paragraphs [0850] and [0851]) and that antagonists, such as antagonistic antibodies that specifically bind Neutrokin- α would be able to inhibit each of these activities (see, e.g., paragraphs [0053] and [0331]).

These statements are presumptively accurate, and have been corroborated by the use of post filing date-data. Applicants remind the Examiner that the use of post filing-date data to corroborate the enablement of a claim is in accordance with relevant case law. The Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id.*, citing *In re Marzocchi*, 439 F2d. 220 at 224 n.4. Indeed, Applicants assertions that Neutrokin- α stimulates lymphocyte proliferation, differentiation and survival have been substantiated by post filing-date data. In the following discussion, the literature names of Neutrokin- α including "BAFF" and "BLyS" will be used. Emphases are added in the following four paragraphs.

MacKay et al.¹ (cited as reference A57 on the PTO/SB-08 submitted August 20, 2001) state that "[a]t equal cell concentration, splenocytes isolated from BAFF-Tg [BAFF-transgenic] mice *survived* longer in culture when compared with control splenocytes" (p. 1703, left column); "BAFF is a powerful cytokine affecting B cells, and *has consequences for T cell* and dendritic cell status." (p. 1706, top of right column); "The presence of large germinal centers in secondary lymphoid organs of BAFF-Tg mice, *higher total T cell numbers* in the spleen and MLN [mesenteric lymph node] as well as increased proportion of both CD4 and CD8 effector T cells in the periphery, and the quality of RF isotypes strongly suggest the active participation of T cells in the immune reactions triggered in BAFF-Tg mice." (p. 1708, lower left column).

¹ MacKay et al., Mice Transgenic for BAFF Develop Lymphocytic Disorders Along with Autoimmune Manifestations, *The Journal of Experimental Medicine* (1999) 190:1697-1710.

Parry et al.², (cited as reference A61 on the PTO/SB/08 submitted August 20, 2001) characterize Neutrokin-alpha as a "growth factor that *promotes B cell proliferation and differentiation*" (p. 401 right column, top).

Do et al.³, (cited as reference A50 on the PTO/SB/08 submitted August 20, 2001) teach that "[a]ttenuation of apoptosis by BLyS is not restricted to B cells after activation by antigen or CD40L, as BLyS also prolongs the *survival* of high density B cells after antigen challenge in vivo (data not shown) and naïve resting B cells in vitro (Figure 7)." (p. 962 right column, middle).

Huard et al.⁴, (provided herewith as Exhibit A) conclude that "it can be said that BAFF regulates both B and T cell activation, with an overall enhancement of *proliferation and effector responses* (Ig secretion for B cells and cytokine secretion for T cells)." (p. 6230, right column, middle). The induction of cytokine or immunoglobulin secretion is an indication the T or B cells have undergone a differentiation step.

Taken together these results confirm Applicants assertions that Neutrokin-alpha is able to stimulate lymphocyte proliferation, differentiation, or survival. Moreover, Applicants submit that by using or routinely modifying assays disclosed in the specification or otherwise known in the art, one of skill in the art, enlightened by the teachings of the specification, can readily determine whether a candidate antibody inhibits lymphocyte proliferation, differentiation, or survival. Accordingly, Applicants submit that the claims as amended, are fully enabled and respectfully request that this rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

B. The Examiner has rejected claims 85-91, 118-124 and 165-173, and 174-180 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. More particularly, the Examiner alleges:

[t]he claim language encompasses treatment of 'any and all' autoimmune diseases, while the disclosure only sets forth for stimulation of B cells and antibodies to Neutrokin-alpha. Applicants extrapolate these two aspects and assert that

² Do et al., Attenuation of Apoptosis Underlies B Lymphocyte Stimulator Enhancement of Humoral Immune Response, *The Journal of Experimental Medicine*, (2000) 192:953-964.

³ Parry et al., Pharmacokinetics and Immunological Effects of Exogenously administered Recombinant Human B Lymphocyte Stimulator (BlyS) in Mice, *The Journal of Pharmacology and Experimental Therapeutics*, (2001) 296:396-404.

⁴ Huard et al., T cell costimulation by the TNF Ligand BAFF, *The Journal of Immunology*, (2001) 167:6225-6331.

antibodies to Neutrokin-alpha inhibit its ability to stimulate B cell proliferation and this assertion has been found to be persuasive. However, the specification is not enabling for a method of treatment of all autoimmune disorders. (Paper No. 13, lines 13-18).

Preliminarily, Applicants point out that claims 118-124, 165, and 173-183 are directed to methods of treating a particular autoimmune disease, namely rheumatoid arthritis or systemic lupus erythematosus and therefore should not be included in this rejection. Therefore, Applicants request that this rejection as it applies to claims 118-124, 165, and 173-183 be reconsidered and withdrawn.

With respect to the remaining rejected claims, Applicants point out that the specification discloses that Neutrokin-alpha antagonists, such as antagonistic antibodies, can be used to treat autoimmune diseases (see, for example, paragraphs [0050] and [0620] in the substitute specification submitted with Applicants' last response). Applicants reiterate that objective enablement is all that is necessary to enable the claimed methods and that post filing date data may be used to confirm that the specification was enabling when filed.

As detailed above and in Applicants' response of May 3, 2002, Applicants specification informs the skilled artisan that 1) Neutrokin-alpha's biological activities have effects in both B lymphocyte and T lymphocyte compartments; and 2) that antagonists can be used to treat autoimmune diseases thereby informing one of skill in the art that either excess Neutrokin-alpha levels and/or excessive Neutrokin-alpha activity (though not necessarily Neutrokin-alpha protein levels) would be present in autoimmune diseases. Post filing-date data corroborates the objective enablement of Applicants' disclosure by confirming the activity of Neutrokin-alpha on lymphocytes (see above); that increased levels of Neutrokin alpha correlate with murine models of autoimmunity⁵ as well as with human autoimmune syndromes such as Rheumatoid Arthritis⁶, Systemic Lupus Erythematosus⁷, and Sjögren's Syndrome⁸; and that administration of a Neutrokin-alpha antagonist, for example, soluble forms of Neutrokin-alpha receptors such as TACI-Fc or BAFF-Receptor 3, alleviates the symptoms of autoimmune disease in murine models of autoimmunity^{9,10}. These facts

⁵ Gross et al., *Nature* (2002) 404:995-999 cited as reference A51 submitted August 20, 2001.

⁶ Cheema et al., *Arthritis Rheum.* (2001) 44:1313-1319 cited as reference B5 submitted May 3, 2002.

⁷ Zhang et al., *Journal of Immunology* (2001) 166:6-10 cited as reference A69 submitted August 20, 2001.

⁸ Marriette et al., 65th Annual American College of Rheumatology Scientific Meeting, Nov. 2001 cited as reference B6 submitted May 3, 2002.

⁹ Gross et al., *Nature* (2002) 404:995-999 cited as reference A51 submitted August 20, 2001.

corroborate that Neutrokin-alpha blocking agents such as antagonistic Neutrokin-alpha antibodies have use in treating a broad class of autoimmune diseases.

The Examiner further states that the present specification does not provide enough guidance such that one of skill in the art could apply their knowledge of the inhibitory activities of antagonistic antibodies that specifically bind Neutrokin-alpha to the treatment autoimmune diseases. Applicants respectfully disagree.

More specifically, the Examiner states

[t]he specification has not provided any guidance regarding extrapolation from inhibition of B cell proliferation...so one of skill could extend their use for the treatment of autoimmune diseases....in the absence of knowledge of higher levels of Neutrokin-alpha and the role it plays if any, in either rheumatoid arthritis, or SLE, or any other autoimmune disease, at the time the invention has made, one of skill would not reasonably expect the instant antagonistic antibodies to have an ameliorative effect in autoimmune diseases....In the instant case, enablement of all the claims rests on two facts that Neutrokin alpha can stimulate B cell proliferation (at the time of filing) and BAFF is expressed in higher levels in autoimmune diseases (post filing date art). These two facts are not sufficient for one of skill in the art to...effectively treat autoimmune disease because increased B cell activity is not the only criterion of all autoimmune diseases, and Neutrokin-alpha is not the only stimulant of B cells, particularly B cells directed to produce antibodies to self antigens as in autoimmune diseases. (Paper No. 13, page 5, lines 11-15).

Applicants have argued above that the Examiner's belief that all that is enabled is the inhibition of proliferation of B cells by antagonistic antibodies of the invention is incorrect. Instead, Applicants have shown that the specification teaches that Neutrokin-alpha acts on both B and T lymphocytes and that antagonistic antibodies of the invention would be able to inhibit lymphocytes proliferation, differentiation or survival.

It was known at the time of filing that the vast majority of autoimmune diseases involve either a B cell component and/or a T cell component. For example, in *Immunobiology* by Janeway and Travers, a 1994 immunology text book states that

¹⁰ Kayagaki et al., BAFF/BLyS receptor 3 binds the B cell survival factor BAFF ligand through a discrete surface loop and promotes processing of NF-kappaB2. *Immunity* (2002) 10:515-24; submitted herewith as

"[a]utoimmune disease occurs when a specific adaptive immune response¹¹ is mounted against self."¹² Similarly Abbas *et al.*, write that "autoimmune diseases may result from primary abnormalities of B cells, T cells, or both."¹³ Thus, at the time of filing, one of skill in the art would have reasonably expected that the inhibition of lymphocyte proliferation, differentiation or survival via administration of antagonistic anti-Neutrokin-alpha antibodies would have had an ameliorative effect on autoimmune diseases. This point is well illustrated by the fact that Gross *et al.*⁵ above, were motivated to treat the symptoms of autoimmune mice with a Neutrokin-alpha antagonist based on the knowledge of Neutrokin-alpha's biological activities and of elevated levels of Neutrokin-alpha in these mice.

Lastly, Applicants would like to address the Examiner's concern that, the full scope of the claims is not enabled because "the claim language encompasses treatment of 'any and all' autoimmune diseases" (Paper No. 13, page 3, lines 13-14). Preliminarily, Applicants submit that because anti-Neutrokin-alpha antibodies of the invention inhibit lymphocyte proliferation, differentiation or survival, treatment with such antibodies would be expected to have an ameliorative effect on a wide array of autoimmune diseases. Additionally, Applicants respectfully remind the Examiner that it is not a function of the claims to specifically exclude possible inoperative embodiments, and the presence of inoperative embodiments within the scope of a claim does not preclude enablement of the claim. *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569 at 1576 (Fed. Cir. 1984). Section 2164.08(b) of the M.P.E.P., 8th edition, instructs that "the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is required in the art." As pointed out by the Federal Circuit, for enablement, "there must be sufficient disclosure, either through illustrative example or terminology, . . . to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus

Exhibit B

¹¹ An "adaptive immune response" is defined "the response of antigen specific lymphocytes to antigen including the development of immunological memory." Janeway, C. & P. Travers. *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London) 1994. p. G:1; submitted herewith as Exhibit C.

¹² *Ibid* p. 11:14, submitted herewith as Exhibit C.

possess the disclosed utility.” *In re Vaeck*, 947 F2d 488, 496 (Fed. Cir. 1991). Applicants submit that one skilled in the art would be able to identify without undue experimentation, the operative embodiments.

Applicants submit that because the specification discloses that antagonistic anti-Neutrokin- α antibodies will inhibit the proliferation, differentiation and survival of lymphocytes, that elevated levels of Neutrokin- α or excessive activity of Neutrokin- α (in the absence of increased levels of Neutrokin- α protein) are present in autoimmune disease, and that therefore antagonists of Neutrokin- α such as antagonistic antibodies would be useful to treat the broad class of autoimmune diseases, claims 85-91, 118-124 and 165-173, and 174-180 are fully enabled. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

¹³ Abbas et al., *Cellular and Molecular Immunology* (W.B. Saunders Company: Philadelphia) 1991. p. 370, submitted herewith as reference Exhibit D.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present Amendment be entered and made of record in the present application.

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. An early Notice of Allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: 2/12/03



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Yu, et al.**

Application Number: 09/589,288

Group Art Unit: 1646

Filed: June 8, 2000

Examiner: Bunner, B.

Title: **Methods of Treatment Using Antibodies** Atty. Docket No. PF343P3C5
to Neutrokin-alpha (as amended)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The application was amended as follows.

In the Claims:

Claims 181-182 were cancelled without prejudice.

Claims 124, 148, and 158 were replaced with the following amended claims:

124125. (New) The method of claim 123 wherein the label is a radioisotope selected from the group consisting of:

- (a) ^{125}I ;
- (b) ^{121}I ;
- (c) ^{131}I ;
- (d) ^{112}In ; and
- (e) $^{99\text{m}}\text{Tc}$.

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148. (Twice Amended) A method of inhibiting lymphocyte leukocyte proliferation, differentiation or survival comprising administering to an individual, a therapeutically effective amount of an antagonistic antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 to 284; and
the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284.

158. (Twice Amended) A method of inhibiting lymphocyte leukocyte proliferation, differentiation, or survival comprising administering to an individual, a therapeutically effective amount of an antagonistic antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.